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Modulating Emotional Experience Using Electrical Stimulation of the Medial-Prefrontal Cortex: A Preliminary tDCS-fMRI Study

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Objectives: Implicit regulation of emotions involves medial-prefrontal cortex (mPFC) regions exerting regulatory control over limbic structures. Diminished regulation relates to aberrant mPFC functionality and psychopathology. Establishing means of modulating mPFC functionality could benefit research on emotion and its dysregulation. Here, we tested the capacity of transcranial direct current stimulation (tDCS) targeting mPFC to modulate subjective emotional states by facilitating implicit emotion regulation.

Materials and Methods: Stimulation was applied concurrently with functional magnetic resonance imaging to validate its neurobehavioral effect. Sixteen participants were each scanned twice, counterbalancing active and sham tDCS application, while undergoing negative mood induction (clips featuring negative vs. neutral contents). Effects of stimulation on emotional experience were assessed using subjective and neural measures.

Results: Subjectively, active stimulation led to significant reduction in reported intensity of experienced emotions to negatively valenced ($p = 0.005$) clips but not to neutral clips ($p > 0.99$). Active stimulation further mitigated a rise in stress levels from pre- to post-induction (sham: $p = 0.004$; active: $p = 0.15$). Neurally, stimulation increased activation in mPFC regions associated with implicit emotion regulation (ventromedial-prefrontal cortex; subgenual anterior-cingulate cortex, sgACC), and in ventral striatum, a core limbic structure (all $ps < 0.05$). Stimulation also altered functional connectivity (assessed using whole-brain psychophysiological interaction) between these regions, and with additional limbic regions. Stimulation-induced sgACC activation correlated with reported emotion intensity and depressive symptoms ($rs > 0.64$, $ps < 0.018$), suggesting individual differences in stimulation responsivity.

Conclusions: Results of this study indicate the potential capacity of tDCS to facilitate brain activation in mPFC regions underlying implicit regulation of emotion and accordingly modulate subjective emotional experiences.

Keywords: emotion regulation, fMRI, medial-prefrontal cortex, stimulation, tDCS

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Implicit regulation of emotions refers to involuntary, automatic inhibition of arousal, and responses to emotionally salient stimuli (1,2). Accumulating evidence suggest that such processes involve primarily regions in the medial-prefrontal cortex (mPFC), specifically ventromedial-prefrontal cortex (vmPFC), and subgenual anterior-cingulate cortex (sgACC), as well as additional salience regions in anterior/mid insula (2–5). These mPFC regions are thought to exert regulatory effects, including decrease of negative affect, via interactions with core limbic structures, primarily amygdala, and ventral striatum (VS), together forming a cortical-subcortical network of implicit control of emotion (4,6–9).

Diminished capacity to adaptively regulate emotions may lead to disturbed mental health (10,11). Indeed, emotion dysregulation is a hallmark feature of various psychiatric disorders, including depression, bipolar, and anxiety disorders (2,12–15). These disorders have

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been associated with aberrant mPFC functionality and its functional connectivity to related limbic structures, further supporting its key role in regulation of emotions (14,16–18). Establishing means to causally modulate mPFC functionality may therefore benefit research exploring the neural circuitry underlying the evolvement of emotional experiences and their regulation, and aid in future development of neuroscience-guided therapeutics for disorders associated with emotion dysregulation (12,19).

One way to modulate brain activity is through transcranial direct current stimulation (tDCS), a noninvasive neuromodulation method used to causally influence cortical activity by inducing transient, low currents between electrodes placed on the scalp (20–24). tDCS research to date has focused predominantly on modulating activity in dorsal/lateral cortical regions involved in cognitive or motor functions (24–27). However, the effect of tDCS on emotional processing has remained largely unexplored, with extant research restricted mainly to top-down explicit regulation (28–30).

A significant obstacle to effective noninvasive neuromodulation application is that the effect of stimulation on specific brain activity is rarely measured during stimulation, since the vast majority of stimulation studies are conducted without ongoing measurement of neural activity. This complicates attempts to empirically test specific hypotheses, and limits effective application of stimulation. Complementing brain stimulation methods with simultaneous neuroimaging enables researchers to identify specific neural regions or processes affected by tDCS, alongside assessment of concurrent changes in relevant behavior (31). Such validation is particularly important as the extent of the effect of stimulation on targeted brain regions and on cognitive functions is critically debated (32,33) but see (34). Furthermore, measuring individual patterns of neural responses to stimulation can help identify inter-individual differences in stimulation responsivity, an aspect of tDCS research typically overlooked.

While combining brain stimulation and imaging methods is crucial for validating the effect of stimulation on brain activity, such studies are particularly challenging since an effective electrode alignment may not be known in advance. Computational models predicting current flow (35) may provide initial indications for electrode alignment; however, the complex, context-dependent, large-scale network nature of brain activity underlying specific functions makes it difficult to predict whether the targeted functions will indeed be modulated. At the same time, imaging-based target validation may incur considerable costs, particularly when new domains are tested for which no prior findings can provide empirical guidance. To resolve this conflict, exploratory studies using multiple, converging measures may provide initial indications for viable research directions and study protocol acceptability and integrity, acquire preliminary estimates for sample size, and point to methodological issues, particularly when introducing a novel experimental design (36,37). To our knowledge, no tDCS-imaging studies have tested whether stimulation can modulate mPFC activity related to emotional experiences.

Here, we conducted a trial to test whether tDCS targeting the mPFC can facilitate processes of implicit regulation of induced negative emotional experiences, using concurrent functional magnetic resonance imaging (fMRI) scanning to validate the effect of stimulation on targeted regions. Sixteen healthy participants were each scanned twice, in a cross-over, sham-controlled, double-blind design in which stimulation was applied during viewing of film clips featuring negative or neutral emotional content. The effect of stimulation was assessed using subjective measures of emotional intensity and stress, and changes in blood-oxygen-level dependent (BOLD) activity and functional connectivity in the targeted regions associated with implicit regulation. To further explore the potential clinical utility of stimulation for symptoms related to mood dysregulation, we examined associations between levels of depressive symptoms and neural responsivity to stimulation. We hypothesized that, specifically during negative emotion induction, active vs. sham stimulation would: 1) reduce the intensity of experienced negative emotions and stress; and 2) increase activation in specific mPFC regions associated with implicit control of emotion (vmPFC and sgACC), and decrease activity in core limbic structures (amygdala and VS). In addition, to explore factors relating to individual differences in neural responsivity to stimulation in the context of emotion regulation, we examined whether depressive symptoms levels, which are related to the capacity to recruit negative affect regulation circuitry (12), would be associated with differences in stimulation-induced recruitment of targeted mPFC regions. Positive results would indicate the potential capacity of tDCS to facilitate brain activation in mPFC regions underlying implicit regulation of emotion and accordingly modulate subjective emotional experiences.

MATERIALS AND METHODS

Participants

Nineteen healthy participants (nine females; $M_{age} = 24.7$ years, $SD_{age} = 2.3$) were recruited. All participants completed screening questionnaires to ascertain they did not have any neurological or psychiatric disorders or contraindications to MRI or tDCS (20). All participants had normal or corrected-to-normal vision, and provided written informed consent approved by Tel Aviv Sourasky Medical Center (TASMC) Ethics Committee and conformed to the Code of Ethics of the World Medical Association (Helsinki Declaration). Participants were paid in exchange for participation. Two participants aborted participation midway through the first scanning session due to claustrophobia; data were also not collected for another participant due to technical problems. Thus, our final sample consisted of 16 participants (seven females; $M_{age} = 25.6$ years, $SD_{age} = 2.5$), each scanned twice.

Emotion Induction Task

The emotion induction task consisted of presentation of short video clips containing emotional or neutral content (38). Videos are increasingly being used to robustly induce emotion in laboratory settings, in part due to their dynamic, immersive nature (39,40). The task stimuli consisted of two equivalent sets of 20 clips each. Each clip was a 9-sec extract from a full-length feature film, featuring human actors in either arousing emotional negative content (e.g., frightening or violent scenes; emotional clips) or neutral content (neutral clips). See Supporting Information for additional information and validation.

Each run of the task (Fig. 1a) consisted of the presentation of one of the 20-clip sets, in one of two pseudo-random sequences (set, sequence orders were counterbalanced across participants). Participants were instructed to view each clip as they may be questioned about their content later, and were not instructed to employ any emotion regulation strategy since the focus of the study was on implicit, automatic regulation. Following each clip, a slide was presented for 9 sec prompting the participant to rank the intensity of emotion they experienced in response to the clip (scale of 1–4, using MR-compatible four-button response box). A 30-sec rest was given after the tenth clip during which the screen was blank. Clips were presented without sound. Participants were given two practice trials.

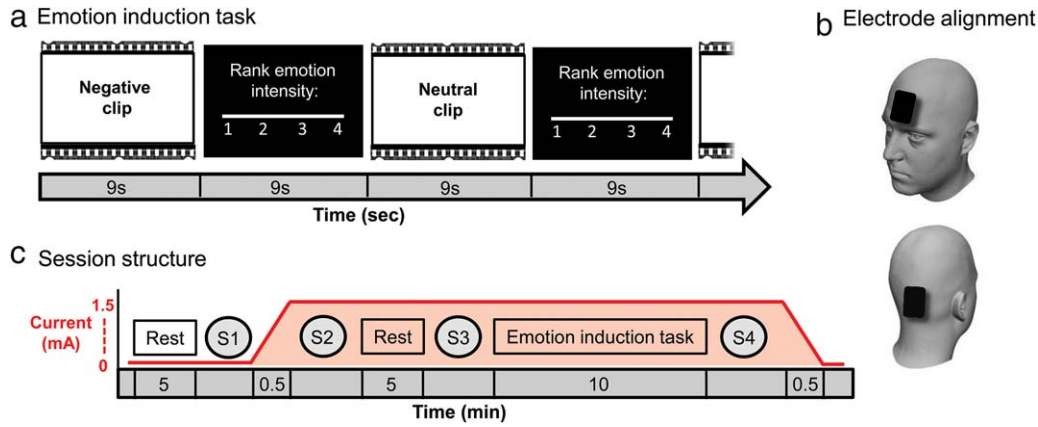

Figure 1. Trial structure, electrode alignment, and session structure. (a) Trial structure in the emotion induction task, which included negative-valence and neutral clips, each followed by a ranking of intensity of emotion elicited by the preceding clip. (b) Electrode alignment during the session: anode electrode in the front, return electrode in the back. (c) Session structure, in terms of current intensity applied (mA, in red), time (min), and task (squares and circles). S1–S4 refer to stress assessments. mA, milliampere. [Color figure can be viewed at wileyonlinelibrary.com]

The task lasted approximately 10 min, including instructions and practice.

Stress levels were assessed at different time points (see Procedure) using a computerized visual analog scale ranging from 0 (not anxious at all) to 30 (extremely anxious) (41).

Electrical Stimulation

Electrical stimulation was applied in the scanner during fMRI acquisition using an MR-compatible system (DC-Stimulator MR, neuroConn GmbH, Germany), via two 5 × 7 cm electrodes with 5 kΩ resistors with high-chloride gel. To facilitate activity in the ventral region of mPFC, the anodal electrode (which facilitates cortical activity) was placed vertically on the forehead (Fig. 1b), its side edges equidistant from the eyes, and the bottom edge 1 cm above the nasion. The return electrode was placed vertically on the back of the head, its top edge aligned with the inion (42). This montage predicts current flow in the targeted regions, as visually estimated from available computational modeling software (35), and confirmed by a study applying more detailed quantification of modeled current flow (supraorbital–occipital montage in Ref. 43).

In the active stimulation condition, a constant 1.5 mA current was delivered for 20 min, with 30 sec of ramp-up and -down at the beginning and end of stimulation, respectively. In the sham condition, stimulation was applied for only 30 sec. Experimenters were blind to stimulation conditions as these were programmed and carried out automatically. A stimulation debriefing questionnaire was administered following each session to assess tolerability and blindness to rule out potential confounding effects related to sensation of stimulation; see Supporting Information).

Levels of Self-Reported Depressive Symptoms

To examine the potential relation between mood dysregulation-related symptoms and neural responsivity to stimulation in emotion regulation circuitry, we administered the Beck Depression Inventory (BDI-II) (44) before the first stimulation session. This 21-item self-report inventory measures current characteristic attitudes and symptoms of depression. Each item is answered on a four-point scale from 0 to 3, with higher scores indicating more severe depressive symptoms. It possesses strong psychometric properties (45). Here, its internal consistency was $\alpha = 0.92$.

PROCEDURE

Each participant completed two study sessions reflecting a within-subject stimulation/sham design. To avoid potential stimulation after-effects (21,22), the two identical sessions were conducted one week apart with the exception that active stimulation was used in one, and sham stimulation in the other (in counterbalanced order).

Upon arrival to the first session, each participant provided written informed consent, and completed the BDI questionnaire. Next, in each session, stimulation electrodes were placed on the participant's head. Following entry into the scanner, electrodes were connected to the stimulator via MR-compatible cords.

Each MRI session (Fig. 1c) started with the first assessment of stress (S1). Then, stimulation was initiated without informing the participant, and approximately 1 min later stress was measured again (S2) to assess whether the initiation of stimulation led to a rise in stress levels. Next, participants were again instructed to rest for 5 min, to allow for stimulation effects to emerge (22). The emotion induction task then followed, with stress assessments before and after the task (S3 and S4, respectively). Finally, an anatomical scan was conducted. Upon exiting the scanner, participants completed the stimulation debriefing form (see Supporting Information).

fMRI Acquisition

Imaging was performed by a GE 3T Signa Excite scanner using an eight-channel head coil. Functional whole-brain scans were performed with gradient echo-planar imaging sequence of functional T2*-weighted images (TR/TE = 3000/35 msec; flip angle = 90°; FOV = 200 × 200 mm; slice thickness = 3 mm; no gap; 39 interleaved top-to-bottom axial slices per volume). Anatomical T1-weighted 3D axial SPGR echo sequences (TR/TE = 7.92/2.98 msec; flip angle = 15°; FOV = 256 × 256 mm; slice thickness = 1 mm) were acquired to provide high-resolution structural images.

fMRI Preprocessing and Analysis

Preprocessing and statistical analyses were conducted using BrainVoyager QX version 2.8 (Brain Innovation, Maastricht, the Netherlands). A detailed description of the preprocessing stages and individual-level analysis is provided in Supporting Information. A group whole-brain, random-effects general linear model (GLM) was

then computed which included four regressors of interest representing all combination of Stimulation (Sham, Active) and clip Valence (Neutral, Emotional) conditions and corresponding to the epochs of clip viewing. Parameter estimates (beta values) were averaged across all voxels within each identified cluster and for each condition. A voxel-wise false discovery rate (FDR)-corrected threshold of $\alpha \leq 0.01$ for mean voxel activation was used, in combination with a cluster-wise threshold of $k \geq 50$ voxels (3*3*3 mm), allowing for a desired balance between type-I and -II error rates (46,47).

First, we tested a Stimulation × Valence interaction in a whole-brain design to identify regions in which stimulation modulated activity explicitly associated with processing of emotional stimuli. Since no significant clusters emerged for this interaction, we then restricted our search to regions demonstrating responsivity to stimulation; i.e., clusters emerging from the main effect of Stimulation. Of the clusters showing stimulation responsivity, we then tested the Stimulation × Valence interaction only in clusters encompassing the primary nodes of the implicit regulation system, namely vmPFC, sgACC, amygdala, and VS (2) which constituted our regions of interest (ROIs). Of note, this approach follows previous studies, e.g., (48,49), and is not prone to selection bias since main and interaction effects are independent in this design (48–50). Nevertheless, caution is still advised when interpreting these results as they emerged following restriction of the search domain.

To further explore observed stimulation-induced effects on emotion-related brain activity, we conducted follow-up analyses within the ROIs. These are described in Supporting Information.

Functional Connectivity Analysis

A whole-brain psycho-physiological interaction (PPI; see Supporting Information) (51,52) random-effects GLM analysis was conducted to assess differences in functional connectivity between ROIs, as a function of stimulation condition. Regressors included: 1) the stimulation condition, 2) the physiological variable, i.e. the time-course activity in the seed ROI, and 3) the interaction variable, i.e., an element-by-element product of the first and second regressors. The psychological and physiological variables were included as confounds of no-interest (in addition to the nuisance regressors mentioned above).

All hypotheses testing were two-sided. Effect sizes are reported using partial eta-squared and Cohen's *d* statistics. Significant effects in fMRI analyses were first determined at a stringent voxel-wise FDR threshold of $\alpha \leq 0.01$, followed by a 50-voxel cluster size threshold. Interaction effects within ROIs and behavior- and symptom-related effects were determined at a more lenient threshold of $\alpha \leq 0.05$, but were Bonferroni-corrected to account for multiple comparisons, to maintain a balance between diminishing the probabilities of type-I as well as type-II errors in such an exploratory study, particularly as the magnitude of effect of stimulation on behavior was expected to be limited (32). Sensitivity to behavioral effects is particularly critical since research on optimizing stimulation application in terms of effects on behavior is lacking, and effects may still not be sufficiently robust (32), whereas effects on emotion are studied even less.

RESULTS

Stimulation-Induced Changes in Subjective Experience

Intensity of subjective emotion experienced in response to the clips was assessed during each task session by averaging intensity rankings for negative and neutral clips separately. The capacity of stimulation to influence emotion intensity was assessed using a repeated-measures analysis of variance (ANOVA), with Stimulation (Sham, Active) and Valence (Neutral, Emotional) as within-subject factors. This analysis yielded a significant main effect of Valence, $F_{1,15} = 149.8$, $p < 0.001$, $\eta_p^2 = 0.91$, whereby viewing negative clips was associated with greater reported emotion intensity relative to neutral clips. This confirms that emotion induction in the task was successful.

This main effect was qualified by a significant Stimulation × Valence interaction (Fig. 2a), $F_{1,15} = 5.95$, $p = 0.028$, $\eta_p^2 = 0.28$. Post hoc dependent-samples *t*-tests revealed that for negative clips, active stimulation was associated with lower experienced emotional intensity relative to sham, $t_{15} = 3.34$, $p = 0.005$, $d = 0.54$, whereas stimulation had no effect on emotion intensity for neutral clips, $t_{15} < 0.01$, $p > 0.99$, $d < 0.01$.

To examine the effect of stimulation on pre- to post-induction stress increase, stress level scores before and after the task (S3 and S4 in Fig. 1c, respectively) were subjected to a repeated-measures ANOVA with Stimulation (Sham, Active) and Time (Pre-task, Post-task) as within-subject factors. This analysis revealed a significant Stimulation × Time interaction, $F_{1,15} = 5.77$, $p = 0.030$, $\eta_p^2 = 0.28$ (Fig. 2b). Follow-up analyses showed a significant increase in stress in the sham condition, $t_{15} = 3.42$, $p = 0.004$, $d = 0.47$, indicating that the task induced an increase in reported stress in this group. In contrast, no significant increase in stress was noted in the active

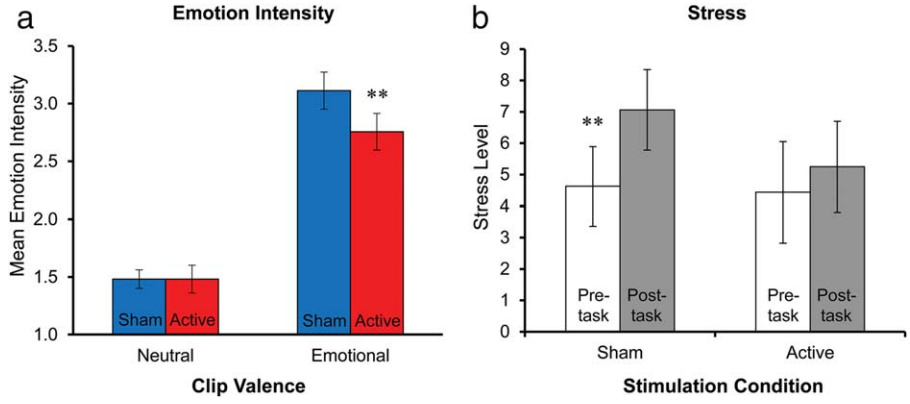

Figure 2. Effects of stimulation on subjective measures. (a) Mean ratings of experienced emotional intensity in response to presented clips, as a function of clip valence (neutral vs. emotional) and stimulation condition (sham vs. active). (b) Mean reported stress levels as a function of time (pre- vs. post-emotion induction task) and stimulation condition (sham vs. active). $^{**}p < 0.01$. Error bars signify SEM. [Color figure can be viewed at wileyonlinelibrary.com]

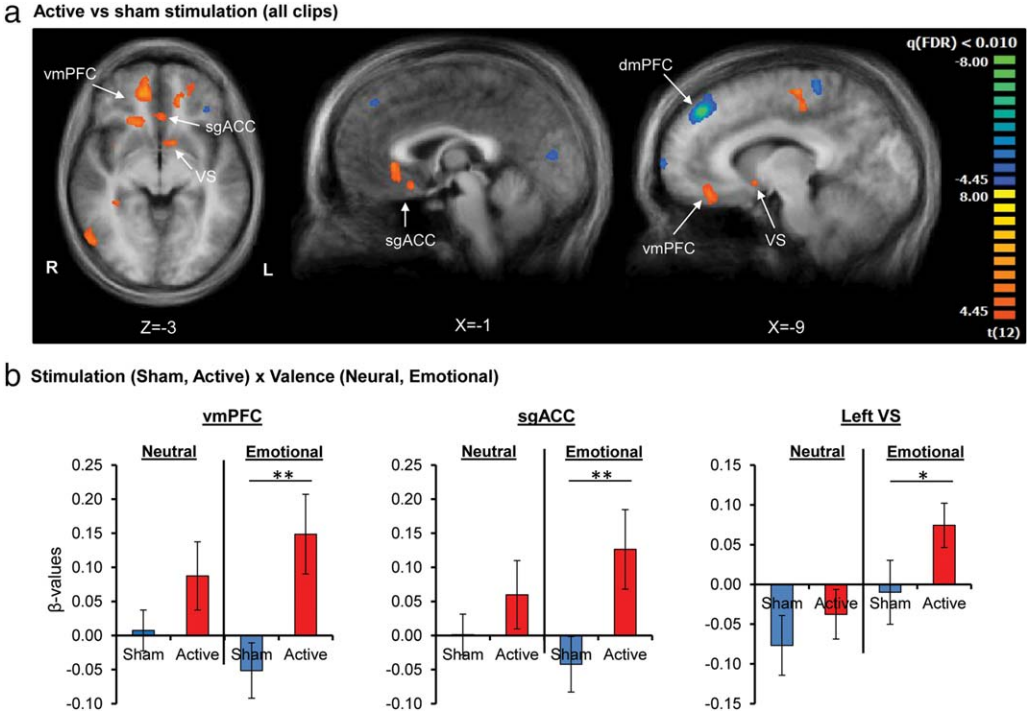

Figure 3. Effects of stimulation on brain activation. (a) Sensitivity to stimulation. Slice views of the results obtained from a whole-brain analysis contrasting *active* minus *sham* stimulation across all presented clips ($p < 0.01$, FDR-corrected, min cluster size $k = 50$ voxels; $n = 13$). (b) ROI analysis for emotion-specific effects of stimulation, for the hypothesized ROIs in which a significant *Stimulation x Valence* interaction was observed. Post hoc analyses revealed that in the vmPFC, sgACC, and VS, active stimulation (relative to sham) significantly increased activity during emotional clips, but not during neutral clips. *$p < 0.05$, **$p < 0.01$. Error bars signify SEM. dmPFC, dorsomedial-prefrontal cortex; sgACC, subgenual anterior-cingulate cortex; vmPFC, ventromedial-prefrontal cortex; VS, ventral striatum. [Color figure can be viewed at wileyonlinelibrary.com]

stimulation group, $t_{15} = 1.52$, $p = 0.15$, $d = 0.15$. These results suggest that active stimulation mitigated an increase in induced stress.

Finally, no differences between the stimulation conditions were noted for any of the debriefing questionnaire items (see Supporting Information). These findings indicate that participants were blind to the stimulation conditions, in line with previous stimulation studies (53).

Stimulation-Induced Changes in Brain Activation

Imaging data for three participants were excluded from the following analyses due to excessive head movements (>4 mm/3°) during at least one of the scanning sessions. Thus, fMRI analyses were performed on 13 participants, each scanned twice. We first tested the Stimulation (Sham, Active) × Valence (Neutral, Emotional) interaction in a whole-brain design. Since no clusters surpassed the whole-brain-corrected threshold for this interaction, we next restricted our search to regions showing sensitivity to stimulation (main effect of Stimulation), and proceeded to test emotion-specific effects in the ROIs defined by this contrast.

General Effects of Stimulation

To identify whole-brain regions sensitive to stimulation in the current experimental context, we contrasted BOLD brain activity across all clips between the active and the sham stimulation scans. Over all, stimulation had a distributed effect on brain activity (Fig. 3a). All clusters surviving the defined threshold (voxel-wise FDR-corrected threshold of $\alpha \leq 0.01$ and cluster-wise threshold of $k \geq 50$ voxels) are listed in Table 1. Notably, we observed stimulation-induced increased activation in clusters within the *a priori* defined ROIs vmPFC, sgACC, and VS.

Emotion-Specific Effects of Stimulation

Stimulation × Valence interactions emerged in three of the targeted ROIs (Bonferroni-corrected, $p \leq 0.05/3$; Fig. 3b). Specifically, a significant interaction emerged in vmPFC, $F_{1,12} = 10.33$, $p = 0.007$, $\eta_p^2 = 0.46$. Follow-up analysis indicated greater activation in this region while viewing the negative clips during active stimulation relative to sham, $t_{12} = 3.25$, $p = 0.007$, $d = 1.25$, while no significant effect of stimulation was observed during neutral clips, $t_{12} = 1.30$, $p = 0.21$, $d = 0.67$. Trend-level interactions were also observed in sgACC, $F_{1,12} = 5.80$, $p = 0.033$, $\eta_p^2 = 0.33$, and VS, $F_{1,12} = 6.10$, $p = 0.029$, $\eta_p^2 = 0.34$, with follow-up analyses showing that activity during negative clips was higher under active relative to sham stimulation ($t[12] = 3.72$, $p = 0.003$, $d = 0.85$, and $t[12] = 2.81$, $p = 0.016$, $d = 0.93$, respectively), but not during neutral clips ($ps > 0.36$, $ds < 0.36$). Of note, the selective effect of stimulation on processing the emotional stimuli was consistent across individual participants (see Supporting Information).

As follow-up exploration of the above effects, we then examined whether the observed changes in subjective emotional experience were directly related to the changes in neural activation induced by active stimulation in vmPFC, sgACC, and VS. The results (see Supporting Information) suggest that greater sgACC response to active stimulation was associated with greater reported emotional intensity.

Individual Differences in Response to Stimulation Associated With Levels of Depressive Symptoms

We next explored whether individual differences in neural response to stimulation during emotional processing in the regions identified above were associated with participants' baseline levels of

Table 1. Effect of Stimulation on Brain Activation.

Region	Hemisphere	BA	X	Y	Z	*t*-value	*p*-value
Active ≥ Sham							
Medial-prefrontal cortex							
vmPFC	R	11/47	8	46	−9	10.25	<0.00001
	L	11/47	−7	37	−15	7.64	0.00001
SgACC	L	32	−1	28	3	7.38	0.00001
	R	32	1	28	0	6.25	0.00006
Lateral prefrontal cortex							
Paracentral gyrus	L	5	−7	−26	48	7.52	0.00001
Middle frontal gyrus	L	11	−25	46	−9	7.42	0.00001
Superior frontal gyrus	R	9	30	48	34	6.54	0.00004
Temporal and parietal cortex							
Precuneus	R	31	14	−57	39	8.67	<0.00001
Middle temporal gyrus	R	37	41	−48	7	7.92	0.00001
Extended limbic							
Anterior insula (ventral)	R	13	35	7	−6	9.21	<0.00001
Head of caudate	R		14	20	2	8.53	<0.00001
Ventral striatum	L		−10	7	−3	7.50	0.00001
Anterior insula (dorsal)	R	13	41	0	11	6.98	0.00002
	L	13	−40	−2	15	6.59	0.00004
Cerebellum	R		29	−53	−36	9.28	<0.00001
Active ≤ sham							
Medial-prefrontal cortex							
dmPFC	L	8	−9	43	44	−10.00	<0.00001
	R	8	8	46	42	−7.15	0.00002
Lateral prefrontal cortex							
Superior frontal gyrus	R	8	20	28	48	−10.58	<0.00001
	L	8	−22	22	51	−7.96	0.00001
Middle frontal gyrus	R	9	56	20	27	−6.59	0.00004
Temporal and parietal cortex							
Middle temporal gyrus	R	20	54	−41	−11	−10.13	<0.00001
Post-central gyrus	R	3	41	−20	42	−8.51	<0.00001
	L	4	−10	−35	60	−7.28	0.00001
Posterior cingulate cortex	R	31	8	−44	32	−8.05	<0.00001
Occipital cortex							
Cuneus	R	30	14	−68	9	−10.69	<0.00001
Subcortical							
Thalamus	L		−23	−29	6	−6.74	0.00003
	L	18	−22	−89	−18	−6.31	0.00006
Cerebellum	R		16	−75	−37	−9.10	<0.00001
	L		−37	−50	−36	−7.01	0.00002

All clusters in the contrast comparing active and sham stimulation across all clips that survived a $p = 0.01$ (FDR-corrected, minimal cluster size of $k = 50$ voxels) threshold. *P*-values refer to activity at peak voxel.
dmPFC, dorsomedial-prefrontal cortex; sgACC, subgenual anterior-cingulate cortex; vmPFC, ventromedial-prefrontal cortex.

depressive symptoms. Results (see Supporting Information) suggest that higher baseline levels of depressive symptoms were associated with increased stimulation-induced sgACC activity while experiencing negative stimuli.

Functional Connectivity

Finally, we conducted exploratory PPI analyses contrasting active with sham stimulation during viewing of the emotional stimuli. The vmPFC, sgACC, and VS clusters were used as seeds in separate whole-brain random-effects analyses. Targets were restricted to clusters identified in Table 1. Table 2 presents the results obtained from the PPI analyses. The stimulation-dependent effects included increased vmPFC-VS and vmPFC-cerebellum coupling, and decreased vmPFC-insula and sgACC-VS coupling. Furthermore, connectivity between VS and amygdala decreased during stimulation.

DISCUSSION

This study explored the potential capacity of tDCS to facilitate implicit regulation of emotion by targeting mPFC functionality. The effect of stimulation was consistently observed across different outcome measures. Active stimulation reduced the intensity of experienced negative emotions, and mitigated a rise in stress levels in response to emotion induction. Concurrent fMRI revealed that stimulation led to increased emotion-related activation in vmPFC, and to a lesser degree in sgACC and VS, and modulated functional connectivity

Table 2. Effects of Stimulation on Functional Connectivity During Emotional Processing.

Seed	Target	X	Y	Z	*t*-value	*p*-value
vmPFC	L cerebellum	−10	−44	−31	9.06	<0.0001
	R anterior insula	35	19	12	−4.68	0.0007
	L VS	−10	10	−9	3.73	0.003
sgACC	L VS	−4	7	−3	−9.96	<0.0001
L VS	R amygdala	17	−2	−12	−4.59	0.0008
	L amygdala	−16	−5	−15	−4.16	0.001

Presented are regions arising from a whole-brain, random-effects functional connectivity analysis using psycho-physiological interaction (PPI) on activity during viewing of negative clips that passed a threshold of $p < 0.005$ (uncorrected). Coordinates are of peak activity, given according to Talairach space.
L, left; R, right; sgACC, subgenual anterior-cingulate cortex; vmPFC, ventromedial-prefrontal cortex; VS, ventral striatum.

between these regions and with additional areas implicated in emotional processing (anterior-insula and amygdala). Directly linking changes in behavior and neural activity, stimulation-induced sgACC activation during processing of emotional stimuli correlated positively with ranking of experienced emotion intensity. Finally, higher levels of self-reported depressive symptoms were associated with higher levels of stimulation responsivity in sgACC, and to a lesser degree in vmPFC, during processing of emotional stimuli.

The main finding of this study is that subjective emotional states may be modulated by noninvasive electrical stimulation. To date, the rapidly growing tDCS literature has primarily targeted processes associated with cognitive and motor domains; here, we provide indication for the susceptibility of the emotional domain to modulation by tDCS. Such application of tDCS may potentially inform emotion and emotion regulation research, as will be discussed later.

The current results also highlight the utility of combining stimulation with concurrent neuroimaging. While noninvasive stimulation techniques are gaining considerable interest as simple and accessible means of influencing brain activity, their potential effective application is generally limited by the difficulty to empirically establish their actual effect on targeted brain regions and networks. Thus, these complementary methodologies can together provide a comprehensive approach for investigating and validating the role of brain systems in cognitive and emotional functions via causal manipulation and concurrent monitoring (31). Importantly, such validation is particularly warranted in light of ongoing debate regarding the extent of the effect of stimulation on physiological and behavioral outcomes (32,33) but see (34). Moreover, these results demonstrate that tDCS may exert its effect on regions that are not in immediate proximity to the stimulation site and influence distributed functional networks. These findings complement transcranial magnetic stimulation (TMS) work demonstrating modulation of functional connectivity between distant brain sites and across large-scale networks (54,55).

The mPFC, and vmPFC and sgACC in particular, has been suggested to comprise key nodes in a cortical system supporting automatic, involuntary regulation of affective states (2,4,56). This system is believed to exert regulatory control via extensive connections between mPFC nodes and limbic regions involved in generation of emotional responses, including VS and amygdala (2,57–59) whose activity and connectivity was shown here to be affected by tDCS. Thus, together with the behavioral findings, our results suggest that stimulation may have influenced subjective emotional experiences by largely facilitating activity in this cortical-subcortical network. The functional modulation of each specific region in this network may distinctly contribute to observed effects, as detailed next.

Increased vmPFC activity coupled with diminished negative valence attributed to stimuli and attenuated stress reports is consistent with findings demonstrating its key role in reducing negative affect and perceived aversiveness of stimuli (2,57,60,61), as well as in reduction of stress response (62,63). Prominent conceptualizations of vmPFC functionality propose that it is a central hub, integrating information from diverse functional neural networks into the construction of subjective affective meaning, and mediating autonomic responses to emotionally salient stimuli (2,17,57,64). Accordingly, vmPFC has been increasingly targeted in recent tDCS research aiming to modulate such functions. For example, tDCS targeting vmPFC has been found to modulate neural processing of pleasant compared to unpleasant scenes (65), fear extinction processes (42), and altruistic action (66). Our results complement such findings, directly demonstrating using concurrent tDCS-fMRI that vmPFC activity can indeed be modulated via stimulation, and suggest that these observed effects may potentially relate to downregulation of negative affect.

Like vmPFC, increased stimulation-induced sgACC activation also co-occurred with reduction in mean reported experienced emotional intensity. However, we noted a positive correlation between sgACC activation and reported negative emotion intensity. Thus, while we aimed to facilitate emotion regulation via increased sgACC activation, these findings suggest that this may have led to the opposite effect. Indeed, accumulating evidence suggests that sgACC activity may mediate negative affect and depressive symptoms, potentially via connections to vmPFC and to subcortical structures including amygdala and VS (14,17,18,67–69). Recently, sgACC functional connectivity with other mPFC regions has been proposed as a biological marker for the efficacy of TMS treatment for depression (69–71), although the nature of desired connectivity pattern has yet to be robustly established. The current findings suggest that function in this region may be modulated directly via electrical stimulation, and that this type of stimulation influences sgACC-VS connectivity. Moreover, higher levels of baseline depressive symptoms were associated with greater sgACC responsivity to stimulation, further relating function in this region to negative affect in general, and depression specifically. Thus, although the net effect of mPFC stimulation led to downregulation of emotion, these results also suggest that stimulation may lead to heterogeneous, region-specific effects on emotion, and as such, caution is warranted when applying stimulation as it may also potentially yield inadvertent effects (42).

Modulated VS activity and VS-amygdala connectivity may have also contributed to the influence on subjective emotional experience. Considered key structures in a *core limbic* system, both VS and amygdala are reliably activated in studies of negative and positive emotion, although their specific role in emotional experience is not yet clear (72,73). Complementing extensive findings linking VS and (more prominently) amygdala activation to negative affect (59,73,74), our results suggest that increased VS activation and decreased VS-amygdala connectivity are associated with an attenuated negative emotional experience. Alternatively, as the VS is strongly associated with reward processing (59,73), these findings may reflect an altered balance between the generation of positive and negative valence, contributing to a change in net subjective emotional experience.

Finally, we also noted decreased dmPFC activation across the task, regardless of content valence. The dmPFC is implicated in mediating negative emotions (4,57,75). For example, the dmPFC is activated during the elicitation of conscious fear or implicit emotional conflict (4,76). This region has direct and indirect connections to subcortical structures implicated in emotional processing, including amygdala and VS (7,77,78), as well as intrinsic connections to vmPFC and sgACC (7,9) via which negative affect has been proposed to arise (75,79) and anti-depressant medication and therapy suggested to influence (71,80,81). Thus, reduced experienced emotional intensity is expected with stimulation-induced decreased dmPFC activation. Of note, dmPFC has been prominently associated with effortful, cognitive strategies of emotion regulation, such as reappraisal, relying on limbic downregulation either directly or via vmPFC connectivity (4,61,82). Importantly, such top-down regulation is posited to involve increased dmPFC activation (4). Our task specifically did not call for explicit regulation of emotion, and, indeed, the effect of stimulation on dmPFC activation was both inhibitory and not emotion-specific, supporting a dissociation from ventral functionality relating to implicit regulation, and suggesting a domain-general effect of stimulation in the current context. Nevertheless, these results suggest that such effortful emotion regulation processes mediated by dmPFC (4) may potentially be targeted by stimulation (83).

The current findings suggest potential implications for tDCS application in the clinical field (84). A hallmark feature of mood and anxiety disorders is diminished ability to adaptively regulate affect and stress, coupled by aberrant neural activity in limbic and emotion regulation regions (12,14,85). Thus, mPFC stimulation may potentially provide the basis for noninvasive therapeutic interventions facilitating emotion regulation processes (86). For example, major depression is clinically associated with pervasive and persistent negative affect, and with functional abnormalities in vmPFC, dmPFC, and sgACC, as well as amygdala and VS (12,14,87). Our results suggest that these regions are susceptible to noninvasive electrical stimulation, and thus, potentially, to therapeutic intervention. Importantly, these findings complement previous efforts to facilitate the regulation of negative affect via TMS targeting mPFC. Specifically, in addition to targeting lateral PFC regions, the dmPFC, vmPFC, and sgACC have been highlighted as direct or indirect targets for TMS application for the treatment of depression- and anxiety-related symptoms (54,69–71,83,88).

Lastly, our results indicate that individual differences in neural responsivity to stimulation in sgACC were associated with levels of self-reported depressive symptoms. As noted above, prior research associates sgACC function with negative affect and depressive symptoms (12,69,70). Our results support this notion, showing that an externally driven increase in sgACC activation to negative-valence stimuli affects more prominently individuals exhibiting increased depressive symptoms. This may further potentially inform therapeutic applications of stimulation in predicting treatment response. Differences in responsivity should be expected for different reasons, e.g., variability in skull thickness, yet such differences are typically overlooked in tDCS research. Quantifying responsivity differences, and factors affecting it, could be used to individually tailor stimulation intensity *in lieu* of a pre-specified, set intensity applied across heterogeneous participant samples (89).

Several important limitations of this study must be noted. First, sample size may likely have limited the statistical power of the analyses performed. The observed effects of stimulation were consistent across individual participants and targeted brain regions, but a larger sample would have contributed to the robustness of the results and could uncover additional effects, particularly for the imaging results for which stringent corrections for whole-brain imaging designs were applied, and effects identified emerged only for restricted search domains. As such, it should be stressed that the current results should be considered preliminary findings suggesting the relevance of this experimental design and methodology to the presented research question. Second, the addition of implicit measures of emotional reactivity, such as skin conductance response, would have contributed to a more comprehensive assessment of emotion modulation. Third, the use of high-definition electrodes in future research may aid in targeting more specific brain regions (90). Fourth, despite the observed effects of stimulation on mPFC function, it is possible that the proximity of the return electrode to the cerebellum may have contributed to the behavioral effects, as this structure has been shown to influence emotional and cognitive processes (91,92). Future studies may consider using an extracephalic location for the return electrode to reduce such potential interference (43). Finally, this study tested only a specific question regarding facilitation of implicit emotion regulation via mPFC stimulation. A more comprehensive design could have explored additional aspects of stimulation or employed various control conditions, a frequently debated topic in stimulation studies. In this vein, future research may wish to explore upregulation of emotion, or the effect of stimulation on positive emotion.

CONCLUSION

Taken together, the results of this study provide indications that subjective emotional experiences may be modulated by tDCS, an effect associated with facilitated mPFC and limbic activation. This presents potential novel opportunities for the application of noninvasive brain stimulation for research on emotion and its regulation. As such, the current results should encourage additional research in this direction, including replication and extension of these findings.

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Authorship Statements

Rany Abend, Yair Bar-Haim, and Talma Hendler designed and conducted the study. Rany Abend, Roy Sar-el, Itamar Jalon, Tal Gonen, and Sharon Vaisvaser collected, analyzed, and interpreted the data. Rany Abend drafted the manuscript, with important intellectual input from Tal Gonen, Yair Bar-Haim, and Talma Hendler. All authors reviewed the manuscript and approved the final manuscript. This work was supported by the Israeli Ministry of Science, Technology and Space. Drs. Daniel S. Pine (NIH) and Gadi Gilam (Tel Aviv University) provided valuable feedback on the manuscript.

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